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10/518,223	12/15/2004	Ning Man Cheng	B001.001.NPRUS	7018

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EAGLE IP LIMITED
UNIT 1201, 12/F KWAI HUNG HOLDINGS CENTRE
89 KING'S ROAD, NORTH POINT
HONG KONG,
CHINA

EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,223	CHENG ET AL.	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/06, 07/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/GB03/02665 filed on 06/20/2003.

The preliminary amendment filed on 5/31/2006 adding new claims 29-34 is acknowledged. Claims 1-34 are pending.

Applicant's election without traverse of Group III, claims 24-28, drawn to a method of treatment of human malignancies, comprising administering human arginase I in the communication filed on 5/31/2006 is acknowledged. Claims 1-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 24-28 and 29-34 are at issue and are present for examination.

Priority

Acknowledgement is made of applicants claim for foreign priority application of CHINA PCT/CN02/00635 of 9/9/2002.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/10/2006 and 7/14/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

Claim 25 is objected to as depending from non-elected claims. Appropriate correction is

required.

For the examination purpose, examiner will read claim 25 as "A method of treatment of human malignancies, comprising administering a pharmaceutical composition comprising an isolated and purified arginase".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 (depends on claim 15) is indefinite in the recitation of "substantially purified" as it is unclear how pure of a polypeptide must be to be encompassed by the phrase "substantially purified". Accordingly, claim 26 is also rejected as dependent on claim 25.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 is indefinite in the recitation of "substantially free of a protein degradation inhibitor" as it is unclear how free of a polypeptide must be to be encompassed by the phrase "substantially free".

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 33 is indefinite in the recitation of "at least approximately 3 days", which is ambiguous and confusing. It is unclear whether applicant meant "at least 3 days"

or "approximately 3 days". In addition, the combination of "at least approximately" is ambiguous and confusing.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 is indefinite in the recitation of "platelet count are below $50,000X10^9$", which is ambiguous and confusing. It is unclear whether applicant meant by platelet count of $50,000X10^9$ per whole body or per liter or per ml. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25, 27-28 and 30-32 are directed to a method of treatment of human malignancies, comprising administering to any patient of any arginase I or any composition comprising any arginase I or any composition that reduces the physiological arginine level. Claim 26 recites the method, wherein said human malignancies are selected from the group consisting of: liver tumor, breast cancer, colon cancer and rectal cancer and claim 27 the method, wherein, the arginase is recombinant. Claim 28 recites the method, wherein pharmaceutical

composition reduces the physiological arginine level in said patient to below 10 uM for at least 3 days and claim 29 recites the method, wherein, pharmaceutical composition comprises human arginase, wherein composition is free of protein degradation inhibitor. Claim 30 recites the method, wherein human patient is monitored for platelet count and claim 31 recites the method, wherein human patient is monitored for prothrombin time. Claim 32 recites the method, wherein said arginase is the sole active ingredients in said composition and claim 34 recites the method, wherein arginine levels in said human is maintained at or below 10uM for at least 3 days. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. As for example, human comprises two kinds of arginase such as arginase I (liver specific) and arginase II (non-liver specific). The specification describe a single species of arginase such as human arginase I. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding the polypeptide having arginine degrading activity. Given this lack of description of representative species encompassed by the genus of proteins used in the methods

of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 25-32 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of human malignancy, comprising administering of a human arginase I of SEQ ID NO: 9 or a composition comprising human arginase I of SEQ ID NO: 9, does not reasonably provide enablement for any method of treatment of any malignancies, comprising administering of any human arginase or any arginase or any composition comprising any human arginase or any composition comprising any arginase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 25-26, 28 and 30-32 are so broad as to encompass any method of treatment of any human arginase or any arginase or any composition comprising any human arginase or any composition comprising any arginase. Claim 26 recites the method, wherein said human malignancies are selected from the group consisting of: liver tumor, breast cancer, colon cancer and rectal cancer and claim 27 the method, wherein, the arginase is recombinant. Claim 28 recites the method, wherein pharmaceutical composition reduces the physiological arginine level in said patient to below 10 uM for at least 3 days and claim 29 recites the method, wherein, pharmaceutical composition comprises human arginase, wherein composition is free of protein degradation inhibitor. Claim 30 recites the method, wherein human patient is monitored for platelet count and Claim 31 recites the method, wherein human patient is monitored for

prothrombin time and Claim 32 recites the method, wherein said arginase is the sole active ingredients in said composition and Claim 34 recites the method, wherein arginine levels in said human is maintained at or below 10uM for at least 3 days. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of arginase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. As for example, human comprises two kinds of arginase such as arginase I (liver specific) and arginase II (non-liver specific). However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one human arginase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass any method of treatment of any malignancies, comprising administering of any arginase or any

composition comprising any arginase because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting arginase activity; (B) the general tolerance of arginase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any arginase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any method of treatment of any malignancies, comprising administering of any arginase or any composition comprising any arginase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any arginase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Vockley et al. (US 6316,199 B1, issue date 11/13/2001). Vockley et al. teach type I human arginase (liver

origin) and a method for treating human cancer including liver cancer, breast cancer by administering arginase polypeptide. Vockley et al. also teach recombinant human arginase, which degrade arginine to ornithine and urea. Vockley et al. further teach a pharmaceutical composition comprising said human arginase for treating said cancer and pegylated the said protein by treating with polyethylene glycol to increase the half-life of the protein in serum and reduce the antigenicity to be an effective therapeutic composition for treating cancer. The composition of Vockley et al. does not comprise nitric oxide producer. Therefore, Vockley et al. anticipate claims 24-27 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 28-29 and 32-34 are rejected under 35 U.S.C. 103 (a) as being obvious over Vockley et al. (US 6316,199 B1, issue date 11/13/2001, see IDS) in view of Tepic et al. (US 6261557 B1, issue date 7/17/2001), see IDS). Vockley et al. teach type I human arginase (liver origin), which degrade arginine to ornithine and urea, followed by reducing the arginine level, and a method for treating human cancer including liver cancer, breast cancer by administering arginase polypeptide. Vockley et al. also teach recombinant human arginase. Vockley et al. also teach a pharmaceutical composition comprising human arginase for treating said cancer and pegylated the said protein by treating with polyethylene glycol (PEG) to increase the half-life of the protein in serum and reduce the antigenicity to be an effective therapeutic composition for treating cancer. The composition of Vockley et al. does not comprise nitric oxide producer. Vockley et al. do not teach lowering physiological arginine level below 10uM for at least 3 days or half-life of the pegylated arginase at least 3 days.

Tepic et al. teach a therapeutic composition comprising a arginine decomposing enzyme similar to arginase, which degrade arginine followed by reducing the arginine level, and modified the enzyme by treating with PEG for treating cancer. Tepic et al. also teach protein degrading inhibitor and method of treating by administering the pegylated enzyme. Tepic et al. also teach use of the said composition to keep the physiological arginine level below 10uM for at least 3 days and half-life of the pegylated arginine-decomposing enzyme is at least 3 days, which is important for the anti-cancer effect of arginine decomposing enzyme.

One of ordinary skill in the art would have been motivated to reduce the arginine level below 10uM because arginine is regarded as the cancer-causing chemical in vivo and by using arginase or arginine decomposing enzyme, one ordinary skill in the art would be able to reduce

the arginine concentration below 10uM, which is the main purpose of this invention, by monitoring arginine concentration that is important for cancer therapy. One of ordinary skill in the art would have been motivated also to use pegylated arginase to increase the half-life of the enzyme for at least 3 days in serum to increase the effectiveness of the enzyme against malignant cell for apoptotic cell death of the malignant cell in order to treat cancer.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to combine the teachings of Vockley et al. and Tepic et al. to make a therapeutic composition comprising human arginase pegylated with PEG as taught by Vockley et al. for treating cancer by administering in a patient and monitoring arginine concentration i.e. 10uM and half-life of the pegylated arginase in the serum i.e. 3 days for treating cancer as taught by Tepic et al.

Conclusion

Status of the claims:

Claims 24-34 are pending.

Claims 24-34 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Iqbal Chowdhury, PhD, Patent Examiner
Art Unit 1652 (Recombinant Enzymes)
US Patent and Trademark Office
Rm. REM 2B69, Mail Box. 2C70
Ph. (571)-272-8137, Fax. (571)-273-8137

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REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1652